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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/548,449	04/13/2000	James Norris	9175-016-999	6716

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EXAMINER	
SCHMIDT, MARY M	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/548,449	NORRIS ET AL.	
	Examiner	Art Unit	
	Mary M. Schmidt	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,10,11,13-16 and 18-33* is/are pending in the application.

4a) Of the above claim(s) *25-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 10-11, 13-16, 18-24, 30-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 April 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4 & 13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims

1. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 23-31 in the specification as originally filed (including the preliminary amendment filed 4/29/2002), have been renumbered as claims 22-30;

Misnumbered claims 33-35 in the amendment filed 4/29/2002 have been renumbered as claims 31-33.

Election/Restriction

2. Applicant's election without traverse of Group I, claims 1-7, 10-11, 13-16, 18-21, 23-25, 31-34, in Paper No. 11, filed 4/29/02, is acknowledged. Please note that after the claims have been renumbered, Group I now embraces claims 1-7, 10-11, 13-16, 18-24 and 30-33, and non-elected Group II embraced claims 25-29. Applicant's further election without traverse of the following species is acknowledged: for claims 6 and 24, the species *chpBK* (note: the restriction requirement mailed 7/17/02 and applicant's response filed 11/25/02 both stated an election of the toxic gene species *chpBK* was for claim 25 (in addition to claim 6); however, there is no *chpBK* species in claim 25, and the restriction is instead applied to claim 24, which has the *chpBK* toxic

agent gene species); for claim 15, the *bacterial specific promoter*; and for claim 16, the *anr promoter*.

3. Renumbered claims 25-29 (previously improperly numbered claims 29-30) are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 11, filed 4/29/02.

Pending claims for examination on the merits below are claims 1-7, 10-11, 13-16, 18-24 and 30-33.

Specification

4. The abstract of the disclosure is objected to because it is more than 150 words. Correction is required. See MPEP § 608.01(b).

5. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

If applicant desires priority under 35 U.S.C. 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant

application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

In the instant case, the priority to U.S. Application 09/291,902, now U.S. Patent 6,271,359, needs to be reflected in the first line of the instant specification.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claim 1 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3-5 of U.S. Patent No. 6,271,359. Although the conflicting claims are not identical, they are not patentably distinct from each other because .

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make a recombinant nucleic acid comprising a nucleotide sequence encoding one or more toxic agents operably linked to a pathogen-specific or tissue-specific promoter, wherein the toxic agent is constructed into a sequence encoding a ribozyme cassette comprising one or more autocatalytically cleaving ribozyme sequences (instant claim 1) since claims 3-5 of U.S. Patent 6,271,359 taught a recombinant nucleic acid comprising a nucleotide sequence encoding one or more toxic agents operably linked to a pathogen-specific promoter, wherein the toxic agent is constructed into a sequence encoding a ribozyme cassette comprising one or more autocatalytically cleaving ribozyme sequence, and wherein the ribozyme cassette is pChop, pSnip and pClip.

One or ordinary skill in the art would have been motivated to make the recombinant nucleic acids comprising a nucleotide sequence encoding one or more toxic agents operably

linked to a pathogen-specific promoter, wherein the toxic agent is constructed into a sequence encoding a ribozyme cassette comprising one or more autocatalytically cleaving ribozyme sequence, and wherein the ribozyme cassette is pChop, pSnip and pClip, as taught in claims 3-5 of U.S. Patent 6,271,359, and thus one of ordinary skill in the art would have been motivated to make the pChop, pSnip and pClip species of compositions embraced by the genus of recombinant nucleic acids comprising a nucleotide sequence encoding one or more toxic agents operably linked to a pathogen-specific or tissue-specific promoter, wherein the toxic agent is constructed into a sequence encoding a ribozyme cassette comprising one or more autocatalytically cleaving ribozyme sequences claimed in instant claim 1.

One of ordinary skill in the art would have had an expectation of success to make the pChop, pSnip and pClip compositions of U.S. Patent 6,271,359, and thus one of ordinary skill in the art would have had an expectation of success to make those pChop, pSnip and pClip species of the compositions embraced by instant claim 1.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-7, 10-11, 13-16 and 18-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-7, 10-11, 13-16 and 31-33 are drawn to recombinant nucleic acid compositions comprising anucleotide sequence encoding one or more toxic agents operably linked to a pathogen-specific or tissue-specific promoter, wherein the toxic agent is constructed into a sequence encoding a ribozyme cassette comprising one or more autocatalytically cleaving ribozyme sequences (**claim 1**); wherein the nucleic acid comprises more than one toxic agent (**claim 2**); wherein the toxic agent is a toxic gene product, such as an Addiction system toxin, or a chromosomally encoded bacterial toxin, such as *chpBK* (**claims 3-6**); wherein the toxic agent is an antisense RNA, such as a DicF1-like antisense RNA (**claims 7 and 10**); wherein at least one toxic agent is adjacent to trans-acting ribozyme and at least one toxic agent is toxic gene product (**claim 11**); wherein the toxic agent is sense RNA (**claim 13**); the sense RNA is targeted to an essential antisense molecule (**claim 14**); the promoter is a bacterial specific promoter (**claim 15**); the pathogen-specific promoter is an anr promoter (SEQ ID NO:3) (**claim 16**); the ribozyme cassette comprises a 5' autocatalytically cleaving ribozyme sequence and a 3' autocatalytically cleaving ribozyme sequence (**claim 31**); wherein one or more autocatalytically cleaving ribozymes has enhances cleavage activity (**claim 32**); wherein the toxic agent is targeted to an antidote (**claim 33**).

Claim 18 is drawn to a vector comprising a recombinant nucleic acid encoding one or more toxic agents operably linked to a pathogen-specific or tissue-specific promoter, wherein the toxic agent is constructed into a sequence encoding a ribozyme cassette comprising one or more autocatalytically cleaving ribozyme sequences.

Claims 19-24 and 30 are drawn to a modified virion comprising a recombinant nucleic acid comprising a nucleotide sequence encoding one or more toxic agents operably linked to a pathogen-specific or tissue-specific promoter, wherein the toxic agent is constructed into a sequence encoding a ribozyme cassette comprising one or more autocatalytically cleaving ribozyme sequences (**claim 19**); which is a bacteriophage (**claim 20**); which is a P1 bacteriophage (**claim 21**); which further comprises a mutated **pac** site (SEQ ID NO:8) or a mutated *pacABC* gene (**claim 22**); wherein the virion has a reduced ability to transfer DNA originating from the virus, and wherein the virion is capable of transferring the recombinant nucleic acid (**claim 23**); wherein the nucleic acid is *chpBK* (**claim 24**); a pharmaceutical composition comprising the modified virion of claim 19, and a pharmaceutically acceptable carrier (**claim 30**).

MPEP 2163 teaches the following conditions for the analysis of the claimed invention at the time the invention was made in view of the teachings of the specification and level of skill in the art at the time the invention was made:

> The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure

of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence....A lack of written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process....Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement....The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

Claims 1-7, 10-11, 13-16 and 18-33 embrace a broad scope of any recombinant nucleic acid comprising a nucleotide sequence encoding one or more toxic agents operably linked to a pathogen-specific or tissue-specific promoter, wherein the toxic agent is constructed into a sequence encoding a ribozyme cassette comprising one or more autocatalytically cleaving ribozyme sequence.

The specification as filed teaches the expression plasmids pChop, pSnip and pClip by way of example. The specification in col. 17, lines 57-63, provide examples of target sequences as ccdA, kis, pemI, parD, phd, higA, chpAI, chpBI, kicA, soc, sos, srnC, flmB, pndB, sof, KorA, korB, korC, korD, korE, or korF transcripts. The specification as filed however, does not teach the target gene nucleic acid sequences.

MPEP 608.01 (p) A. states that "[a]n application as filed must be complete in itself in order to comply with 35 U.S.C. 112.... "Essential material" is defined as that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention.... In any application which is to issues as a U.S. patent, essential material may not be incorporated by reference to... (2) non-patent publications." In the instant case, to describe the claimed invention, one of skill in the art must first know the nucleic acid sequence of any such target gene that would be toxic upon inhibition since design of the claimed toxic ribozyme sequences is based on complementary nucleic acid binding principles and the nucleic acid sequence of the target molecule must be known in order to determine the complementary sequence via Watson-Crick base pairing. Thus the target gene sequence is considered "essential material" to the claimed invention.

The MPEP 608.01 (p) A. continues to state that "[m]ere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by 35 U.S.C. 112, first paragraph.... In addition to other requirements for an application, the referencing application should include an identification of the referenced patent, application, or publication. Particular attention should be directed to specific portions of the referenced document where the subject matter being incorporated may be found."

In the instant case, Applicant has not provided any specific reference to a representative number of species of the genus of *any and all* possible "toxic agent" sequences. Absent such

specific direction in the specification as filed, the claims as written are not adequately described for the essential description of the breath of claimed toxic agent ribozymes to target gene sequences.

The design of ribozyme molecules to any pathogen or tissue target gene requires the specific description in the specification of the target nucleic acid sequences from which to design by complementary base pairing, the antisense oligonucleotide (having the opposite, or "antisense" base sequence from the genomic, "sense" strand of the target). One of skill in the art would not have known what the nucleic acid sequence structure of a representative number of species of the genus of *any* possible pathogen or tissue target gene nucleic acid sequence was from the disclosure of the gene names alone (such as those in col. 17, lines 56-63). One of skill in the art would not have recognized that applicant was in possession of a representative number of species of ribozyme constructs, vectors comprising the ribozyme constructs, pharmaceutical compositions of the ribozyme constructs, nor virions comprising the claimed toxic ribozyme compositions, absent the specific description of the target gene sequences and direction of identifying characteristics (such as regions of the target nucleic acid) from which one skilled in the art would have had been able to envisage specific nucleic acid sequences from which to design complementary ribozyme oligonucleotide sequences having the claimed functions. Absent this critical description, which would have provided the physical and/or chemical properties of the target gene sequence, one of skill in the art would not have recognized that

applicant was in possession of a representative number of species of the claimed genus of ribozyme compositions claimed.

Similarly for claims 2-6, 11, 13-14, drawn to compositions of claim 1 comprising toxic gene products, Addiction System toxin, chromosomally encoded bacterial toxins, and where the toxic agent is a sense RNA and the target is an essential antisense molecule, one of skill in the art would not have recognized that applicant was in possession of a representative number of species of the claimed toxic genes, Addiction System toxin sequences, chromosomally encoded bacterial toxin sequences or toxic agent genes absent further description in the specification as filed of the physical and structural characteristics (i.e. nucleic acid sequences) that have the claimed functions. Neither the specification as filed nor the prior art provides a clear definition of any such sequences so that the nucleic acid composition is immediately visualized. Furthermore, since such sequences are considered "essential material" to the claimed invention, a representative number of species of the indicated toxic genes should have been described in the specification as filed. The specification as filed does teach in col. 42, lines 53-57 and col. 43, Table 1, specific target gene sequences to the *E.coli* tRNA-asp, *Streptomyces* secA, *Enterococcus* ftsZ, *Pseudomonas* dnaG, *Streptomyces* rpoA, *Staphylococcus* tRNA-Asp, pol II, HBV, RB, IGF1, SH, Pol I, HPV, C3, C9, and Tel sequences. These sequences are not considered representative of any eukaryotic, bacterial or pathogen target sequence as broadly claimed since based on the knowledge of these sequences alone, one of skill in the art would not be able to envision any other viral, bacterial, or eukaryotic gene sequences.

10. Claim 30 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprising the modified virion of claim 19 and a pharmaceutically acceptable carrier, does not reasonably provide enablement for pharmaceutical compositions comprising the modified virion of claim 19, and a pharmaceutically acceptable carrier. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 30 is drawn to a pharmaceutical composition comprising the modified virion of claim 19, and a pharmaceutically acceptable carrier. Since the claim is drawn to a "pharmaceutical composition" is has implied use in a whole organism for treatment purposes. Please not that removal of the word "pharmaceutical" from the preamble of the claim would overcome the instant rejection.

The specification as filed teaches the pClip, pChop, and pSnip ribozyme constructs, but does not teach virions including the claimed constructs, the ribozyme expression constructs, having a use in a whole organism for therapeutic effects.

There is a high level of unpredictability known in the antisense art, and the analogous ribozyme art, for therapeutic, *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the whole organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and

simultaneously avoid non-specific binding (see Branch). Note also Ma et al. who teach (on page 167) that "to gain therapeutic advantage using antisense-based technology, ODNs must have certain characteristics. They must be resistant to degradation, internalize efficiently, hybridize in a sequence specific manner with the target nucleic acid, display adequate bioavailability with a favorable pharmacokinetics profile and be nontoxic." Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Flanagan teaches, "oligonucleotides (*in vivo*) are not distributed and internalized equally among organs and tissues.... Unfortunantly, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)." Ma et al. supports the difficulties of *in vivo* use of ODNs on pages 160-172. Jen et al. further taught that "given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive. While a number of phase I/II trials employing ONs have been reported..., virtually all have been characterized by a lack of toxicity but only modest clinical effects." (Page 315, col. 2) Green et al. summarizes that "the future of nucleic acid therapeutics using antisense ODNs ultimately depends on overcoming the problems of potency, stability, and toxicity; the complexity of these tasks should now be apparent. Improvements in delivery systems and chemical modifications may lead to safer and more efficacious antisense compounds with improved pharmacokinetics and reduced toxicities."

(P. 103, col. B) Note also some of the major outstanding questions that remain in the art taught by Agrawal et al. On page 79, col. 2.

In vitro, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Note also Ma et al. who teach that "*in vitro* subcellular distribution is dependent on the type of ODN modification, cellular system and experimental conditions. ODNs, once internalized, are distributed to a variety of subcellular compartments." (Page 168) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." Note Jen et al. who teach that "although mRNA targeting is impeccable in theory, many additional considerations must be taken into account in applying these strategies in living cells including mRNA site selection, drug delivery and intracellular localization of the antisense agent." (Abstract) Bennett et al. further taught that "although the antisense paradigm holds great promise, the field is still in its early stages, and there are a number of key questions that need to be answered and technical hurdles that must be overcome....The key issues concerning this class of chemicals center on whether these compounds have acceptable properties as drugs. These include pharmacokinetics,

pharmacological and toxicological properties." (Page 13) As argued above, these issues remain unpredictable in the art for antisense oligonucleotide administration *in vivo*.

One of skill in the art would not accept on its face the successful delivery of the disclosed virions comprising ribozyme nucleic acid molecules *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art. Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of ribozyme molecules in whole organisms. Specifically the specification does not teach (1) stability of the ribozyme molecule *in vivo*, (2) effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for the unpredictable factors stated above for whole organism use of the breath of claimed nucleic acids would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed.

11. The claims are free of the prior art since the prior art did not teach nor fairly suggest recombinant nucleic acid compositions comprising toxic agents operably linked to a pathogen-specific or tissue-specific promoter, wherein the toxic agent is constructed into a sequence

encoding a ribozyme cassette comprising one or more autocatalytically cleaving ribozyme sequences, vectors comprising such compositions, or virions comprising such compositions.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to Katrina *Turner*, whose telephone number is (703) 305-3413.

M. M. Schmidt
February 9, 2003

SEAN McGARRY
PRIMARY EXAMINER
1635